Remarks

Applicant cancel non-elected claims 1-36, 38-88, and 94-106 without prejudice or disclaimer of the subject matter recited therein, and expressly reserve all rights to such subject matter. Applicants have amended claim 37, and have added claims 107-31. Upon entry of this amendment, claims 37, 89-93 and 107-31 will be pending. The office action is discussed below.

The claims are definite

On page 3 of the office action, the examiner rejected certain claims on indefiniteness grounds. More specifically, the examiner considered the terms "cell" and "host cell" to be indefinite because the structures of the cells are not disclosed. The examiner also alleged to that essential subject matter is missing from the claims because the claims do not set forth the structural arrangement between the cells, target antigen and cytokine, chemokine, etc. Applicants respectfully traverse these rejections.

For definiteness, a claim need only reasonably apprise those skilled in the art of the utilization and scope of the invention. *Hybritech, Inc. v. Monoclonal Antibodies,* 231 USPQ 81, 94-95 (1986). Words are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01. Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. *See* MPEP § 2111. In sum, in order to reject the claims on definiteness grounds, it is incumbent on the

examiner to show how and why the skilled person having applicants' specification would not be apprised of the invention by the language-at-issue.

In the instant situation, the skilled person could turn to the specification and determine that host cells should be able any capable of expressing the nucleic acid sequences as recited, and include APC and antigen presenter precursor cells, monocytes, macrophages, dendritic cells, Langerhans cells, tumor cells, B-cells, etc. See, e.g, page 27, lines 2-4 and page 42, lines 20-29. Accordingly, the skilled person would not be confused by what is meant by a "cell" or "host cell."

Turning to the issue of structural relationships, applicants submit that the amended and new method claims clearly spell out structural relationships in a manner understood by the person skilled in the art.

In view of the foregoing, applicants respectfully request withdrawal of the rejections.

The claims do not cover a product of nature

On pages 3-4 of the office action, the examiner rejected claim 37 under 35 USC § 101 as covering a product of nature. Claim 37, however, recites a recombinant vector, which exists only by way of human intervention. Accordingly, claim 37 cannot cover a product of nature, and therefore the rejection should be withdrawn.

The claims stand enabled

On pages 4-6 of the office action, the examiner rejected the claims on enablement grounds. Essentially, the examiner avers that the claims cover areas such as gene therapy or vaccines to treat all tumors or infectious diseases, which are unpredictable. Applicants respectfully traverse these rejections.

Section 112 mandates that patent applications contain the "manner and process of making and using" the invention. The courts have considered applications in compliance with section 112 where the person of skill in the art can practice the invention without undue experimentation. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). The test is not whether experimentation is necessary, but whether any experimentation would be undue in view of what type and amount of experimentation is usual in that particular field. *See* MPEP §§ 2164.05 (a-b), 2164.06 (Rev. 1, February 2003). Routine design choices cannot be equated with non-enablement.

Thus, the burden to establish an enablement rejection rests with the Examiner. *See* MPEP §§ 2164.01; 2164.04 (Rev. 1, February 2003). As explained by the Federal Circuit in considering the intertwined issues of enablement and utility:

> [I]t follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the inventor's asserted utility. * * * Taking these facts – the nature of the invention and the PTO's proffered evidence – into consideration we conclude that one skilled in the art

> would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO has not satisfied its initial burden. ***Accordingly, applicants should not be required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112.***

In re Brana, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (emphasis added), *citing In re Marzocchi*, 169 USPQ 367, 369-70 (CCPA 1971).

Applicants submit that the Examiner has not met this burden, as explained below.

Applicants' specification contains a wealth of data showing the effectiveness of the claimed invention. Examples 24-27 discuss the co-stimulation and T-cell proliferation effects of embodiments of the claimed invention. Example 28 demonstrates desirable effects on apoptosis, which is known to involved in cancer. Example 29 discusses anti-tumor effects of embodiments of the invention. Examples 30-33 also contain positive data on co-stimulation using embodiments of the invention. This data has not been addressed by the examiner, and applicants cannot be compelled to substantiate this data absent evidence from the examiner that the data is somehow insufficient. *See supra In re Brana*. Applicants therefore submit that the claimed invention is enabled, and that enablement is supported by the data in the specification. Accordingly, applicants request withdrawal of the rejections.

Double patenting

On page 6-7 of the office action, the examiner rejected the claims on double patenting grounds over claims 1-6 of U.S. Patent No. 6,548,068. Applicants note that these type of rejections are intended to prevent an impermissible "prolongation" of the patent term caused by multiple patents possessing claims that are obvious in view of one another. That is, the claimed subject matter must be sufficiently close that issuance of more than one patent would necessarily result in a prolonged term for the same inventive concept. Accordingly, in making an obviousness-type double patenting rejection, the examiner must indicate how the claims of the instant application are sufficiently "obvious" over the other claims so as to result in an impermissible prolongation of patent term. The examiner, however, has not made out a *prima facie* case why the claims are obvious in view of one another, and therefore the rejection should be withdrawn.

The invention is not taught by the prior art

On pages 7-13 of the office action, the examiner rejected the claims as anticipated by several references. Applicants respectfully traverse these rejections.

Applicants note that in order to reject a claim under 35 USC § 102, the examiner must demonstrate that each and every claim term is contained in a single prior art reference. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986); *see also* MPEP § 2131 (August 2001). Claim terms are to be

given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (August 2001). Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. *See In re Zletz*, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) (holding that claims must be interpreted as broadly as their terms reasonably allow); MPEP § 2111 (August 2001).

Not only must the claim terms, as reasonably interpreted, be present, an allegedly anticipatory reference must enable the person of ordinary skill to practice the invention as claimed. Otherwise, the invention cannot be said to have been already within the public's possession, which is required for anticipation. *See Akzo, N.V. v. U.S.I.T.C.*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986); *In re Brown*, 141 USPQ 245, 249 (CCPA 1964). Applicants review below the references with these concepts in mind.

Zajac

On page 7, the examiner rejected claim 37 as anticipated by the Zajac paper. The Zajac paper discloses a recombinant vaccinia that expresses a tumor-associated antigen and a B7 molecule. The Zajac paper, however, does not disclose the co-expression of ICAM-1 and LFA-3 in addition to B7, as required by the claims. Accordingly, Zajac cannot anticipate the claims.

Chen EP

On pages 7-8, the examiner rejected claim 37 as anticipated by the Chen EP. The Chen EP discloses a tumor cell transfected to express B7 and a CD2 ligand. The Chen EP, however, does not disclose the co-expression of ICAM-1 and LFA-3 in addition to B7, as required by the claims. Accordingly, the Chen EP cannot anticipate the claims.

Oertli

On page 8, the examiner rejected claim 37 as anticipated by the Oertli paper. The Oertli paper discloses a recombinant vaccinia that expresses a B7.1 and/or B7.2 molecule. The Oertli paper, however, does not disclose the co-expression of ICAM-1 and LFA-3 in addition to a B7 molecule, as required by the claims. Accordingly, Oertli cannot anticipate the claims.

Pestka PCT

On page 8, the examiner rejected claim 37 as anticipated by the Pestka PCT. The Pestka discloses a tumor cells that are modified to express B7 molecules, various interferons and interleukin, TNF and ICAM-1, for example. The Pestka PCT, however, does not disclose and enable the co-expression of LFA-3 in addition to B7 and ICAM-1, as required by the claims. Accordingly, the Pestka PCT cannot anticipate the claims.

Parra

On page 8, the examiner rejected claim 37 as anticipated by the Parra paper. The Parra paper discloses a variety of recombinant CHO cells, but not one that co-expresses B7, ICAM-1 and LFA-3, as required by the claims. See the paragraph bridging the left and right column on page 509 of Parra. Accordingly, the Parra paper cannot anticipate the claims.

Goldbach-Mansky

On page 9, the examiner rejected claims 37 and 89 as anticipated by Goldbach-Mansky. Goldbach-Mansky discloses the K562 erythroleukemic cell line, which is stated to naturally express a number of molecules. This cell line, however, is not infected, transfected or induced with a recombinant vector, as required by the claims. Accordingly, Goldbach-Mansky cannot anticipate the claims.

Young

On pages 9-10, the examiner rejected claim 37 as anticipated by Young. Accoridng to the examiner, Young discloses that human dendritic cells naturally expressed B7, ICAM-1 and LFA-3. These cells, however, are not infected, transfected or induced with a recombinant vector, as required by the claims. Accordingly, Young cannot anticipate the claims.

Radmayr

On page 10, the examiner rejected claim 37 as anticipated by Radmayr. Radmayr, like Young, discloses that human dendritic cells naturally express a number of surface molecules. These cells, however, are not infected, transfected or induced with a recombinant vector, as required by the claims. Thus, Radmayr cannot anticipate the claims.

Hargreaves

On page 11, the examiner rejected claim 37 as anticipated by Hargreaves. Hargreaves discloses cells transformed to express B7 and one other MHC class II alloantigen. See pages 1512 at the beginning of the discussion section. Hargreaves does not tech expression of B7, ICAM-1 and LFA-3 in a cell infected, transfected or induced with a recombinant vector, as required by the claims. Accordingly, Hargreaves cannot anticipate the claims.

Vyth-Dreese

On pages 11-12, the examiner rejected claim 37 as anticipated by Vyth-Dreese. Vyth-Dreese, like the Radmayr and Young references discussed above, discloses that immortalized T lymphocytes naturally express a number of surface molecules. These cells, however, are not infected, transfected or induced with a recombinant vector, as required by the claims. Thus, Vyth-Dreese cannot anticipate the claims.

Wyss-Coray

On page 12, the examiner rejected claim 37 as anticipated by Wyss-Coray. Wyss-Coray discloses that antigen presenting cells naturally express a number of surface molecules. These cells, however, are not infected, transfected or induced with a recombinant vector, as required by the claims. Thus, Wyss-Coray cannot anticipate the claims.

Delabie

On pages 12-13, the examiner rejected claims 37 and 89 as anticipated by Delabie. According to the examiner, Delabie discloses that Reed-Sternberg cells naturally express B7, ICAM-1 and LFA-3. These cells, however, are not infected, transfected or induced with a recombinant vector, as required by the claims. Thus, Delabie cannot anticipate the claims.

Cunningham

On page 13, the examiner rejected claim 37 as anticipated by Cunningham. Cunningham discloses that alveolar epithelial cells naturally express a number of surface molecules. These cells, however, are not infected, transfected or induced with a recombinant vector, as required by the claims. Thus, Cunningham cannot anticipate the claims.

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Applicants note the examiner's discussion about product-by-process claims when the examiner relies upon characterization studies of non-engineered cells (see, for example, the rejections based on Young and Radmayr). It is important to remember that the prior art studies were performed in order to elucidate the biological mechanisms naturally occurring in those cells, and thus the skilled person in performing those studies would not seek to genetically modify those cells. The instant claims, however, are the antithesis of these studies because the claims require that the nucleic acid sequences that encode B7, ICAM-1 and LFA-3 be introduced into the host cell by way of a recombinant vector, which are not used when one is studying natural cells.

The diverging approaches and goals of the present invention as compared to the prior art results in structural differences between the claimed subject matter and the naturally-occurring cells that have been previously studied. Accordingly, the claimed cells differ from the prior art cells in ways in addition to the processes by which the cells were made or attained.

The claimed invention is not suggested by the prior art

On pages 14-15 of the office action, the examiner rejected claims 37 and 89-93 as obvious over the Schlom '802 patent in view of Radmayr. Schlom was cited for disclosing a recombinant vaccinia virus vector that expresses a B7 molecule and an antigen. The examiner stated that Schlom did not disclose the use of vectors encoding other co-stimulatory molecules. The examiner then relied upon Radmayr to provide such a teaching. Applicants respectfully traverse this rejection.

At the outset, applicant(s) note that the examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43 (August 2001). Thus, the examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416,

419-20 (Fed. Cir. 1986). The references are discussed with these legal concepts in mind.

Although Schlom provide excellent and useful vaccinia vectors, there is no teaching in Schlom to proceed in the manner attempted by the examiner. The examiner looks to Radmayr to provide dendritic cells that express a number of surface molecules. The examiner, however, does not explain why, much less how, the skilled person would make recombinant vectors that express B7, LFA-3 and ICAM-1 from Radmayr's naturally-occurring cells. Radmayr already provides a naturally occurring cell. Why would the skilled person seek to engineer a recombinant cell to express the antigens already allegedly expressed by Radmayr? This point is not addressed by the examiner. Accordingly, applicants submit that the examiner has not made out motivation or suggestion to combine the references, and thus there is no proper *prima facie* case of obviousness. Absent a suggestion or motivation to combine, the reference can only be combined via a proscribed hindsight reconstruction of the prior art. The rejection calls to mind the Federal Circuit decision of *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998), where the court explained:

> As this court stated, "virtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); *see also Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations and mostly of old elements"). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit

> an examiner to use the claimed invention itself as a blueprint to defeat the patnetability of the claimed invention. Such an approach would be an "illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996).
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventors and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

Applicants submit that the rejection does not satisfy the strictures of the *Rouffet* decision, and therefore the rejection should be withdrawn.

Request

Applicants submit that the claims are in condition for allowance, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,

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